IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Gunnar Aberg et al.

Serial: 10/069,663

Filed: October 26, 2006

For: OPTICALLY ACTIVE ISOMERS OF KETOTIFEN AND THERAPEUTICALLY ACTIVE METABOLITES THEREOF

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents P.O. Box 1450, Alexandria, VA 22313-1450 on November 2, 2006 (Date)

Kevin S. Lemack
Name of applicant, assignee, or Registered Representative

Signature

November 2, 2006
Date

DECLARATION UNDER 37 C.F.R. § 1.132

The Honorable Commissioner
Of Patents & Trademarks
Washington, D.C. 20231

Sir:

I, Thomas Walle, declare:

THAT I am a citizen of Sweden, a permanent resident of the USA, and resident of Charleston, Charleston County, South Carolina;

THAT I am Professor of Pharmacology at the Medical University of South Carolina, Charleston, SC. From 1964 to 1968, I was Lecturer at the Department of Analytical Chemistry, Royal Institute of Pharmacy, Stockholm, Sweden; from 1968 to 1970, I was a Postdoctoral Fellow at the Department of Analytical Chemistry, Royal Institute of Pharmacy, Stockholm, Sweden; from 1970 to 1972, I was Assistant Professor of Pharmacology and Experimental Medicine at the University of Cincinnati College of Medicine, Cincinnati, OH; from 1972 to 1974, I was Assistant Professor of Pharmacology, Medical University of South Carolina, Charleston, SC; from 1974 to 1978, I was Associate Professor of Pharmacology, Medical University of South Carolina, Charleston, SC; and since 1978, I am Professor of Pharmacology at the Medical University of South Carolina, Charleston, SC;

THAT I am a graduate of the Royal Institute of Pharmacy, Stockholm, Sweden from which I hold a Ph.D. degree (equivalent) in Organic Analytical Chemistry (1968) and a degree as a Licensed Pharmacist (1965);

THAT I have thirty-five years of academic experience and medical research;

THAT I am an author of about 200 publications on various medical topics;

THAT I have made numerous scientific presentations on the subjects of drug metabolism;

THAT I have reviewed the Office Action dated August 4, 2006 in the above referenced Application. I have also reviewed the application in the present case and the art cited by the Examiner in his rejection;

THAT several metabolic studies on ketotifen and analogs of ketotifen have been performed under my supervision;

THAT the purpose of my studies on ketotifen were to investigate the enzymatic metabolism of ketotifen and in particular the formation of norketotifen from ketotifen in human liver microsomes and human liver cells; and

THAT I have made the following observations and conclusions:

Several metabolic studies on ketotifen and on the formation of norketotifen were performed in my laboratories under my close supervision about six years ago. It was found that numerous metabolites of racemic ketotifen are formed as a result of the metabolism of ketotifen in human liver microsomes and human liver cells. One of the metabolites being formed was norketotifen.

At the time these studies were performed, I was not aware that atrop-isomers of norketotifen could exist. It was at that time assumed that the methyl-group on the piperidine nitrogen of ketotifen was pivotal for the formation of chirally stable atropisomers of ketotifen. Thus, we assumed that the metabolism of S-ketotifen or R-ketotifen may result in the formation of achiral norketotifen.

Subsequently, I have learned that chemically stable atropisomers of norketotifen actually can be made synthetically, and that these atropisomers have different pharmacological activities, which of course indicates chiral stability in vivo of the atropisomers S-norketotifen and R-norketotifen. S-norketotifen has more anti-inflammatory potency than R-norketotifen and interestingly and to my surprise, there are even differences between the side effects of these two atropisomers of norketotifen. Thus S-norketotifen has surprisingly been found to be totally devoid of the dominating side effects of the parent compound ketotifen, which is the dose-limiting sedation of ketotifen.

It is not at all predictable whether atropisomeric S-norketotifen is formed in vivo from atropisomeric pure S-ketotifen, for the following reasons:

(1) I am unaware of the performance or results of any studies investigating the metabolism of the pure atropisomers S-ketotifen of R-ketotifen.

(2) Thus, nothing is known about stereoselective oxidative demethylation of the atropisomers of R- or S-ketotifen or regarding the formation of the atropisomer S-norketotifen from atropisomeric S-ketotifen.

(3) The *in vivo* metabolism leading to this type of demethylation is a complicated metabolic pathway in the human liver with many intermediate steps and it is not possible to determine the actual events without further detailed metabolic and analytical investigations.

(4) A very large number of enzymes called racemases or epimerases that interfere with various metabolic processes are expressed in the liver and it can be expected that

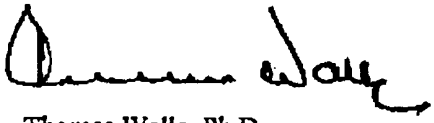
intermediates in the metabolism of S-ketotifen may be subjected to inversion or racemization. This often becomes very complicated, as is the case with the isomers of ketoprofen, where one of the isomers, but not the other, may be inverted in the liver in certain species (Aberg et al. Inversion of (R)- to (S)-ketoprofen in eight animal species. Chirality, 1995. 7: 383-387 and Jamali, Lovlin & Aberg: Bi-directional chiral inversion of ketoprofen in CD-1 mice. Chirality, 1997,9: 29-31).

(5) Issues concerning inversion and racemization are complicated even for classic chiral isomers (containing a chiral carbon center in the molecule), but with regard to atropisomers, it is even more complicated since atropisomeric parent compounds may very well be metabolized to achiral metabolites (being devoid of atropisomerism) or racemic metabolites (mixture of R-and S-atropisomers).

(6) In conclusion, we did not know that stable atropisomeric norketotifen metabolites existed when we performed our metabolic studies on ketotifen, but we assumed that demethylation of S-ketotifen or R-ketotifen would lead to the formation of achiral norketotifen. Furthermore, it is completely unpredictable whether the metabolism of atropisomerically pure S-ketotifen will lead to atropisomerically pure S-norketotifen since during the metabolic process, S-ketotifen may be inverted (to form R-norketotifen) or racemized (to form RS-norketotifen) or may retain the atropisomeric purity (forming S-norketotifen) or the metabolism of S-ketotifen may result in a mixture of said events.

I further declare that all statements of the foregoing declaration made of my own knowledge are true and that those made upon information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statement may jeopardize the validity of the above-identified application or any patent issuing thereon.

Signed by me on this 29th day of October 2006



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